wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins.

36. (Amended) A method of preparing a lyophilizate, the method comprising mixing a buffered solution containing a monoclonal antibody or a polyclonal antibody, a sugar or an amino sugar, at least one amino acid and a surfactant, to prepare a mixed solution, wherein the mixed solution has a pH value of 5-8; and

lyophilizing the mixed solution, wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins.

REMARKS

Claims 13-36 are pending. In this Response, applicants amend claims 13 and 36.

Claim 26 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner takes the position that claim 26 contains an improper Markush group, since the members within the group do not share a common utility or common structural feature.

This rejection is respectfully traversed.

The Examiner refers to MPEP §803.02 in the rejection of claim 26. However, this section of the MPEP deals with the restriction of Markush claims, not the determination of indefiniteness with regard to a Markush group. Since, in this case, the Examiner has not made a restriction of the Markush group, MPEP §803.02 does not apply. Reference instead should be made to MPEP §2173.05(h).

According to §2173.05(h), Markush groups are acceptable if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. While the materials set forth in a Markush group ordinarily must belong to a recognized physical or a chemical class, or to an art-recognized class, when the Markush group occurs in a claim reciting a combination (such as the present case), it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature that all of them possess this property.

In this case, claim 26 describes the monoclonal antibody which is incorporated into the claimed lyophilizate. The Markush group is directed to the antigen against which the monoclonal antibody acts. It is important to note that applicants are **not** claiming the antigen itself; rather, the monoclonal antibody is being claimed. Thus, each of the members of the Markush group is a monoclonal antibody, each of which possesses the property common to all antibodies. Thus, the Examiner's rejection is improper, and should be withdrawn.

Claim 36 is rejected under 35 U.S.C. §102(e) as being anticipated by Fukuda et al. (U.S. Patent No. 5,908,826).

Fukuda is directed to a freeze-dried preparation containing a monoclonal antibody. According to the disclosure on column 3, line 38 through column 5, line 34, a monoclonal antibody solution is added to a buffer containing gelatin or a carboxylic acid. For the purpose of stabilizing the monoclonal antibody, or for the purpose of adjusting the pH, a monosaccharide, disaccharide, sugar alcohol or amino acid may also be added. See column 4, lines 35-40. The pH value of the solution to be freeze-dried is

from 4.0 to 8.1. See column 5, lines 6-7. Before freeze-drying, it is also possible to add a surfactant. See column 5, lines 28-34.

Pages 5-6 of the present specification disclose that the use of ingredients such as gelatin are not acceptable as stabilizers for pharmaceutical additives. The bottom of page 6 indicates that the object of the present invention is to provide stable pharmaceutical preparations that are free of such ingredients. Therefore, applicants have amended claim 36 to indicate that the lyophilizate is essentially free of additional proteins (thus, avoiding the use of proteins such as gelatin, as disclosed in Fukuda). Applicants have also included the limitation that the lyophilizate is essentially free of polyethylene glycols, to reflect the change previously made to claim 13.

Claims 13-21, 23-32 and 34-35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Phillips et al. (WO 89/11297) in view of Friedman et al. (U.S. Patent No. 5,750,142) and Arizono et al. (1994).

The Examiner relies on Phillips as teaching a lyophilizate comprising a monoclonal antibody, a sugar and an inorganic buffering agent, which is essentially free of polyethylene glycols or additional proteins. The Examiner admits that Phillips does not teach the inclusion of at least one amino acid and a surfactant.

The Examiner relies on Friedman as teaching a lyophilizate comprising an antibody, at least one amino acid and a surfactant. The Examiner takes the position that it would have been prima facie obvious to combine Phillips and Friedman. The Examiner merely relies on Arizono as teaching one of the antigens claimed in claim 26.

This rejection is respectfully traversed. Applicants have the following comments.

Phillips discloses a lyophilized composition containing a monoclonal antibody, a buffer and maltose, a disaccharide. See page 4, lines 2-4. A preferred embodiment of the invention disclosed in Phillips is a formulation containing a buffer having a low pH (between about 3-6), maltose and IgG antibody. Preferred buffers include sodium acetate, phosphate and citrate. See column 7, lines 17-21.

As the Examiner correctly indicated, Phillips does not include at least one amino acid or a surfactant in the lyophilizate disclosed therein.

Friedman is directed to dry compositions which are easily reconstituted with water to form submicron oil-in-water emulsions for use in the administration of pharmaceuticals and cosmetics. Specifically, Friedman discloses a lyophilized composition comprising an amino acid, an emulsifier and an oily component, which upon reconstitution forms an oil-in-water emulsion. See column 2, lines 12-19. If desired, a co-emulsifier, preferably a non-ionic surfactant, can be included in the composition. See column 2, lines 39-41.

According to column 3, lines 3-6, the compositions of Friedman contain no carbohydrates. In the "Background of the Invention" section, Friedman indicates that the use of carbohydrates in lyophilized compositions is disadvantageous, since the carbohydrates may cause hypertonic solutions upon reconstitution and have a high susceptibility for microbial contamination. See column 1, lines 51-55.

Column 5, lines 36-42, indicate that a suspending agent may optionally be included in the compositions to be lyophilized to protect the emulsion during the drying stage, as well as to control the droplet size of the reconstituted emulsion. Suitable

suspending agents include proteins such as gelatin and pectin, and polyethylene glycols.

Claim 34 (which can be found in column 19) indicates that the compositions can contain an antibody.

Applicants submit that Friedman would not have been combined with Phillips at the time of the invention, and that the combination of the two references would not result in the present invention.

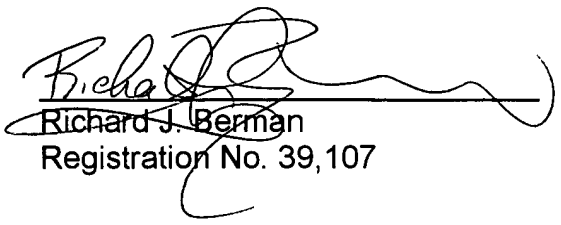
First, Friedman indicates that the compositions disclosed therein contain no carbohydrates, and the reference dissuades their use. Both the present invention and Phillips require the use of a carbohydrate (specifically, a sugar or an amino sugar). Thus, Friedman would not have been combined with Phillips. NO

In addition, as applicants noted above, Friedman discloses that the composition disclosed therein may contain a suspending agent, such as gelatin or pectin (which are each proteinaceous additives) or polyethylene glycols. Claim 13 of the present invention specifically indicates that the lyophilizate must be essentially free of additional proteins and polyethylene glycols. Thus, the combination of Friedman and Phillips would not result in the present invention.

Since the combination of Friedman and Phillips would not have been made by one of ordinary skill in the art at the time of the invention, and such a combination would not result in the present invention, applicants submit that the rejection is improper. Applicants respectfully request that the rejection be withdrawn.

In the event this paper is not timely filed, applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper.

Respectfully submitted,



Richard J. Berman
Registration No. 39,107

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.,
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

RJB/ccd

Enclosure: Marked-up copy of claims

MARKED-UP COPY OF CLAIMS

13. (Twice Amended) A lyophilizate, comprising

(1) a monoclonal antibody or a polyclonal antibody;

(2) a sugar or an amino sugar;

(3) at least one amino acid; and

(4) a surfactant,

wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins.

36. (Amended) A method of preparing a lyophilizate, the method comprising mixing a buffered solution containing a monoclonal antibody or a polyclonal antibody, a sugar or an amino sugar, at least one amino acid and a surfactant, to prepare a mixed solution, wherein the mixed solution has a pH value of 5-8; and lyophilizing the mixed solution, wherein the lyophilizate is essentially free of polyethylene glycols and additional proteins.